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10/582,099	03/19/2007	Osamu Kanome	03500.103394.	1165

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EXAMINER	
LAM, ANN Y	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,099	KANOME ET AL.	
	Examiner	Art Unit	
	ANN Y. LAM	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,6 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,6 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 3 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. 7,497,997 (hereinafter "Glezer").

Glezer teaches an assay cartridge which incorporates fluidic components such as compartments, , chambers, fluidic conduits, fluid ports/vents, valves, and the like and/or one or more detection components such as electrodes, electrode contacts, sensors (e.g., electrochemical sensors, fluid sensors, mass sensors, optical sensors, capacitive sensors, impedance sensors, optical waveguides, etc.), detection windows. A cartridge may also comprise reagents for carrying out an assay such as binding reagents, detectable labels, sample processing reagents, wash solutions, buffers, etc. The reagents may be present in liquid form, solid form and/or immobilized on the surface of solid phase supports present in the cartridge. Column 37, lines 31-51.

The sample chamber may contain dry reagents used in carrying out the assay that reconstitute on addition of a liquid sample. Column 39, lines 9-36.

The reagent chambers are chambers adapted to hold liquid reagents used during the course of assays carried out in a cartridge. The reagent chamber design considerations for preferred embodiments of a cartridge depend, in part, upon the particular assay(s) to be performed by the cartridge. For example, a cartridge may have one, two or more reagent chambers depending on the number of reagents required by the assay format. Liquid reagents that may be held in a reagent chamber include buffers, assay diluents, solutions containing binding reagents (e.g., proteins, receptors, ligands, haptens, antibodies, antigens, nucleic acids and the like), solutions containing enzymes and/or enzyme substrates, solutions containing control reagents, ECL read buffers, wash solutions, anti-foam agents, extraction reagents and the like. A cartridge may have one, two or more reagent chambers depending, e.g., on the number of reagents required by the assay format. The reagent chamber design considerations for preferred embodiments of a cartridge depend, in part, upon the particular assay(s) to be performed by the cartridge. The reagent chamber is connected to a reagent conduit for transferring reagent from the chamber to other fluidic components in the cartridge. Column 43, lines 19-55.

In one embodiment of the invention, a cartridge has one or more reagent compartments that are empty or contain only dried reagents. Prior to conducting an assay, the user or cartridge reader dispenses liquid reagents into these chambers

which, optionally, reconsititute any dried reagent present in the chambers; the reagents are thus prepared for use in the assay. Column 43, lines 56-65.

Certain assay reagents (especially biological reagents and/or binding reagents such as enzymes, enzyme substrates, antibodies, proteins, receptors, ligands, haptens, antigens, nucleic acids and the like), when dissolved in a liquid medium require special handling and storage in order to improve their shelf life. Reagents that may be included in dry form include biological reagents, binding reagents, pH buffers, detergents, anti-foam agents, extraction reagents, blocking agents, and the like. Column 45, line 52 to column 46, line 22.

Dry reagents may be employed in a cartridge based assay system in a number of ways. As described above, dry reagents may be stored in a reagent chamber that is filled prior to use by a user or by a cartridge reader apparatus. Similarly, dry reagents may be stored in other fluidic components such as within fluidic conduits or chambers, most preferably within a fluidic conduit connecting the sample and detection chambers. Introduction or passage of liquid (e.g., a liquid sample or a liquid reagent) through the conduit or chamber results in dissolution of the dry reagent. Dry reagents may be inserted during the manufacture of a cartridge by depositing the dry reagents in the appropriate fluidic component, e.g., by depositing the reagent in the form of a powder or pellet or by incorporating the dry reagent in a screen printed ink. Alternatively, the reagents may be inserted in solution and then dried to remove the solvent. In one preferred embodiment dried reagents may be formed upon a substrate by depositing solutions containing the reagents in one or more predefined locations and

subsequently drying the reagents to form a dried reagent pill under conditions such that on addition of a liquid sample or an appropriate solvent, the dry reagent dissolves into solution. The term "pill" is used to refer generally to an amount of a dry, but redissolvable, reagent on a substrate and not to connote any specific three dimensional shape. The location of a pill on a substrate is referred to as a "pill zone". The substrate is preferably a component of the cartridge, e.g., cartridge body, chamber, cover layer, electrode array, etc. Suitable locations for the pill zone include the sample chamber, reagent chamber, sample conduits, and reagent conduits so that liquid reagents and samples pick up the dry reagent prior to their introduction to the detection chambers. Alternatively, the reagent pills may be located within the detection chambers themselves. Column 46, lines 23-65.

A pill zone in which dried reagents are deposited may be prescribed by a boundary which confines the volume of a deposited solution (and, therefore, the dried reagent left after allowing the solution to dry) to a specific region of a substrate. According to one preferred embodiment of the invention, a cartridge comprises a pill zone that is bounded by a boundary surface, the boundary surface being raised or lowered (preferably, raised) and/or of different hydrophobicity (preferably, more hydrophobic) than the pill zone. Column 46, line 66 to column 47, line 18.

The pill zone may for example be defined by a depression cut or molded into the substrate. The reagent can then be dispensed onto the substrate within the pill zone boundary and thereafter dried to form the dried reagent pill. Column 47, lines 19-35.

A cartridge may comprise one or more detection chambers. Cartridges comprising multiple detection chambers may comprise separate fluidic systems for each detection chamber (e.g., multiple sample chambers and/or reagent chambers and associated fluidic conduits) so that assays on multiple samples may be carried out in parallel. The two detection chambers may be used to carry out different sets of assays, thus increasing the number of measurements that can be carried out on a sample relative to a cartridge with one detection chamber. Advantageously, the use of multiple detection chambers allows for carrying out in a single cartridge multiple incompatible measurements, that is measurements that can not be performed in a single reaction volume or benefit from being carried out in separate reaction volumes, e.g., measurements that have different requirements for pH or assay composition or otherwise negatively interfere with each other. Column 49, line 53 to column 50, line 5.

Shown in one exemplary embodiment in figure 9 is sample chamber 920, reagent chamber 925, detection chambers 945 or 946 and pill chambers/zones 990 and 991 hold dry reagents and are positioned, respectively, in the fluidic pathway between sample port 920 and detection chambers 945 and 946 so that liquid passing through the chamber/zones will reconsititute the dried reagents and carry the resulting solutions into the detection chambers. Column 54, line 46 to column 55, line 5.

In cartridges for conducting binding assays for analytes of interest, pill zones 990 and 991 preferably comprise labeled binding reagents (e.g., antibodies, nucleic acids, labeled analogs of analytes of interest, etc.), detection chambers 945 and/or 946 comprise one or more immobilized binding reagents (preferably, an array of

immobilized binding reagents, and reagent chamber 925 comprises a wash reagent for removing sample solution and/or unbound labeled reagents from the detection chambers. In embodiments where one of the detection chambers is used for control assays or for assay calibration, the associated pill zone may comprise control reagents such as an added analyte. Column 55, lines 34-48.

The assay reagent in each domain may be the same or may be different. Assay reagents that may be used include, but are not limited to, antibodies, fragments of antibodies, proteins, enzymes, enzyme substrates, inhibitors, cofactors, antigens, haptens, lipoproteins, liposaccharides, cells, sub-cellular components, cell receptors, membrane fragments, viruses, nucleic acids, antigens, lipids, glycoproteins, carbohydrates, peptides, amino acids, hormones, protein-binding ligands, pharmacological agents, membrane vesicles, lipsomes, organelles, bacteria or combinations thereof. Preferably, the assay reagents are binding reagents capable of specifically binding to an analyte of interest or, alternatively, of competing with an analyte of interest for binding to a binding partner of the analyte of interest. Column 5, lines 2-41.

In preferred embodiments, it may be desirable to immobilize (by either covalent or non-covalent means) biomolecules or other assay reagents to carbon-containing materials, e.g., carbon inks, carbon black, fibrils, and/or carbon dispersed in another material. One may attach antibodies, fragments of antibodies, proteins, enzymes, enzyme substrates, inhibitors, cofactors, antigens, haptens, lipoproteins, liposaccharides, cells, sub-cellular components, cell receptors, viruses, nucleic acids,

antigens, lipids, glycoproteins, carbohydrates, peptides, amino acids, hormones, protein-binding ligands, pharmacological agents, and/or combinations thereof. Biological membranes (e.g., cells, cell membranes, membrane fragments, membrane vesicles, lipsomes, organelles, viruses, bacteria, etc.) may be directly adsorbed on carbon without destroying the activity of membrane components or their accessibility to binding reagents. Column 21, line 47 to column 22, line 8.

The assay modules (preferably, assay cartridges) may be used to carry out panels of assays. Suitable panels include panels of assays for analytes or activities associated with a specific biochemical system, biochemical pathway, tissue, organism, cell type, organelle, disease state, class of receptors, class of enzymes, class of pathogen, environmental sample, food sample, etc. Preferred panels include immunoassay for cytokines and/or their receptors, growth factors and/or their receptors, allergen specific antibodies, tumor markers, etc. Preferred panels also include libraries of receptors or ligands (e.g., panels of G-protein coupled receptors, tyrosine kinase receptors, nuclear hormone receptors, cell adhesion molecules (integrins, VCAM, CD4, CD8), major histocompatibility complex proteins, nicotinic receptors, etc.). Preferred panels also include libraries of cells, cell membranes, membrane fragments, reconstituted membranes, organelles, etc. from different sources (e.g., from different cell types, cell lines, tissues, organisms, activation states, etc.) Column 75, line 38 to column 76, line 39.

As to Applicant's claims 3 and 12, the substrate (i.e., component of the cartridge; column 46, lines 23-65) or entire cartridge is equivalent to a cell culture substrate

having an area for culturing a cell. The detection chambers with immobilized binding reagents (column 55, lines 34-48), wherein the binding reagents may be for example cells (column 21, line 47 to column 22, line 8), are equivalent to an area for immobilizing a biologically activity substance having a biological activity to a cell. The portion of the cartridge which includes the pill zone(s) (column 55, lines 34-48) is equivalent to an area for culturing a cell, comprising an area for holding a biologically active substance having a biological activity to the cell. It is noted that the pill zones are capable of functioning as a "culturing area" and is capable of holding a biologically active substance having a biological activity to the cell, since the pill zones are capable of holding for example receptors or ligands, etc, (column 21, line 47 to column 22, line 8; column 75, line 38 to column 76, line 39). Moreover, the pill zones are capable of holding the biologically active substance in such a manner that it is released in a culture liquid when coming in contact with the culture liquid, since the pill zones are capable of holding reagents, as described above, in such a manner that the reagents are reconstituted by a liquid and thus released or control-released in a liquid, such as culture liquid. (It is noted that Applicant has not recited structural features of the holding area or immobilizing area in such a way as to distinguish from the Glezer device.)

(It is also noted that the disclosure of the Glezer patent relied upon in the rejection above is also disclosed in the related provisional application, 60436569, for example, on pages 48-49, and 62, and is thus given the priority date of the provisional application.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over 7,497,997 (hereinafter "Glezer"), in view of 4,378,428 (hereinafter "Farina").

The teachings of Glezer have been discussed above and are applicable to claim 6. Glezer however does not teach that the holding area includes a combination of areas different in a density of the biologically active substance in the holding area, and the immobilizing area includes a combination of areas different in density of the biologically active substance in the immobilizing area.

It is noted however that Glezer does disclose the following. The assay cartridges of the invention may comprise a plurality of flow cells or detection chambers. In certain preferred embodiments the flow cell may comprise the same assay domains or, at least, have at least some assay domains that share specificity for the same analytes of interest. In these embodiments, the plurality of flow cells may be used to analyze a plurality of different samples or to compare samples that have been pre-treated in different ways. Alternatively, one of the flow cells may be a control flow cell used to analyze a control sample and another of the flow cells may be a test flow cell used to analyze a test sample. The control sample may be a completely pre-defined control

sample or may be a mixture comprising the test sample but spiked with added analytes of interest so as to allow for calibration of the assays by the method of standard addition. In an alternative embodiment, the assay cartridge has at least two flow cells that have assay domains for two different assay panels. Advantageously, such a cartridge may be used to separately perform assay reactions that are incompatible with each other. Column 14, lines 13-31.

For example, in one embodiment employing a plurality of detection chambers, one or more of a plurality of detection chambers is used as control/calibration chamber for measuring assay control/calibration samples. In one such embodiment, a first and a second detection chamber are each configured to carry out a panel of one or more assays for one or more analytes. One detection chamber (the test chamber) is used to analyze a sample. The other detection chamber (the control chamber) is used to analyze a spiked sample having a predetermined additional amount of the one or more of the analytes of interest (this predetermined additional amount, preferably, being provided by passing the sample through a reagent pill zone comprising the additional amounts). The change in signal between the two chambers allows for the calculation of the responsivity of the signal to changes in analyte and can be used to calibrate the system and/or to determine if the cartridge is functioning properly. In another embodiment employing a control chamber, the control chamber is not used to analyze the sample or a derivative thereof, but is used to measure analyte in a separate control or calibrator matrix. The signal in the control chamber may be used for determining background signals (by using a matrix with no analyte), for calibrating

the instrument (by using a calibrator matrix with a predetermined amount of analyte to determine calibration parameters) or to determine if the cartridge is functioning properly (by using a control matrix with a predetermined amount of analyte and determining if the signal falls within a predetermined acceptable range). Column 50, lines 6-33.

Examples of using control/calibration reagents picked up in pill zones are also disclosed in column 57, line 63 to column 58, line 50. Kits may include disassembled components necessary to make an assay module of the invention. Alternatively, the kits may comprise, in one or more containers, an assay module of the invention and at least one additional assay reagent necessary to carry out an assay. The one or more assay reagents may include, but are not limited to, binding reagents (preferably, labeled binding reagents, more preferably binding reagents labeled with electrochemiluminescent labels) specific for an analyte of interest, ECL coreactants, enzymes, enzyme substrates, extraction reagents, assay calibration standards or controls, wash solutions, diluents, buffers, labels (preferably, electrochemiluminescent labels), etc. Column 76, lines 40-52.

In a specific example, electrochemiluminescent (ECL) counts are preferably converted to concentrations using predetermined calibration parameters. It should be recognized that conversion to ECL counts can occur in a number of differing ways, including, converting all the acquired data points after acquiring all data, converting each individually acquired data point as it is acquired, converting groups/groupings of acquired data points, etc. Column 71, lines 51-67.

Furthermore, Farina provide details regarding providing a standard control. Farina teach that by utilizing increasing known analyte concentrations, it is possible to construct a standard or reference curve of catalytic activity (e.g., rate of formation of reporter molecule) or alternatively, a function of catalytic activity versus analyte concentration. The standard or reference curve may then be utilized to determine an unknown analyte concentration after measuring the rate of formation of reporter molecule at the same conditions used to construct the standard curve. Column 8, lines 31-40. Further details of the assay, exemplified in competitive format, is discussed in column 8, lines 41-63. It is further discussed that, in the exemplary assay, the concentrations of the antibody, the polypeptide partner and the labeled analyte should be selected in a particular assay so that varying amounts of analyte will be reflected in the conversion of the substrate to the reporter molecule. Column 9, lines 60-66.

It would have been within the skills of the ordinary artisan to use the Glezer device to provide assays using increasing known analyte concentrations, and thus increasing amounts of binding partner (e.g., bound in the detection chamber as disclosed by Glezer), and other necessary reagents (e.g., dried labeled reagents, buffers, etc., in the pill zones as disclosed by Glezer) as necessary to construct a standard curve to determine unknown analyte concentration, as well known in the art, and as disclosed by Farina. It is implied from the Glezer disclosure (as discussed above regarding the pill zones) that different concentration of reagents can be provided in the pill zones. It is within the skills of the ordinary artisan to provide the different concentrations of reagents in the pill zones, such as the preformed zones with

boundaries, in a liquid form for drying, as taught by Glezer. Such different concentration of reagents in the zones of same area provides different densities of the reagents. Likewise, different concentrations of the immobilized biomolecules or reagents in the detection chamber provides different densities of the biomolecules or reagents. Moreover, the skilled artisan would have had reasonable expectation of success since Glezer disclose that multiple different assays may be performed on the device, including calibration or control assays. It is noted that the portion of the device comprising the pill zones of the fluidic circuits of the different assays discussed above is equivalent to the claimed area for holding a biologically active substance, including areas different in density of the biologically active substance. Similarly, the portion of the device comprising the detection chambers is equivalent to the area for immobilizing a biologically active substance including areas different in a density of the biologically active substance.

Response to Arguments

Examiner acknowledges that the claims are put into condition for allowance according to the indication of allowable subject matter in the previous Office action. However, upon further review and search, the above rejections were found appropriate. It is noted that while there are significant differences in the structure of the Glezer invention and the structure of Applicant's invention as described in the detailed specification, the claims however do not include structural limitations such that they

distinguish the claims from the prior art Glezer patent. The present Office action is made nonfinal.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Malmqvist 6,200,814, discloses a gradient of amount of ligands may be provided (col. 14, lines 26-37.)

Ivarrson, 6,493,097, discloses simultaneous monitoring (column 7, line 60 – column 18, line 7) and presenting surface concentration changes (column 23, lines 53-64.)

Tashiro, 7,541,195, discloses a substrate for a microarray, the substrate having protruding spots for immobilizing biomolecules on the top surface of the protruding spots.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANN Y. LAM whose telephone number is (571)272-0822. The examiner can normally be reached on Mon.-Thurs. 9-7:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ann Y. Lam/
Primary Examiner, Art Unit 1641